PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 31954PC01	**FOR FURTHER ACTION** See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/DK 03/00361	International filing date *(day/month/year)* 02.06.2003	Priority date *(day/month/year)* 31.05.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/663		
Applicant K BENHAVNS UNIVERSITET et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.12.2003	01.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Beeck, M Telephone No. +49 89 2399-8473

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00361

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-29 as originally filed

Claims, Numbers

1-15 filed with telefax on 16.06.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	13-15
Inventive step (IS)	Yes:	Claims	1-12
	No:	Claims	13-15
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations

see separate sheet

D1: US-A-4 973 576 (SAKAMOTO SHUICHI ET AL) 27 November 1990 (1990-11-27)

D2: US-A-3 959 458 (AGRICOLA FRANCIS OSWALD ET AL) 25 May 1976 (1976-05-25)

D3: US-A-4 814 326 (ROSINI SERGIO ET AL) 21 March 1989 (1989-03-21)

D4: US-A-5 220 021 (DUNN COLIN J ET AL) 15 June 1993 (1993-06-15)

SECTION V:

1) A "first medical use" of compositions comprising biphosphonic acid derivatives is already known from documents D1 to D4 (see the whole documents).

Therefore the subject-matter of claims 13 to 15 is not novel (Article 33 (2) PCT).

2) Closest prior art document for the assessment of claims 1 to 12 is document D2 which discloses the use of such biphosphonates as anticalculus agents in combination with the anticaries agent i.e. sodium or calcium monofluorophosphate for providing anticaries benefits while avoiding adverse effects on silicate filling materials present in the mouth (see the abstract, examples I, XIV, XV and XVI).

The subject-matter of claim 1 differs from this disclosure in that the biphosphonate is the pharmaceutically active compound for the prevention of secondary caries.

Therefore the problem to be solved by the invention was to provide pharmaceutically active compounds other than fluorophosphates for the treatment of secondary caries.

The solution is to use biphosphonates for this purpose.

Since this was not obvious for the person skilled in the art, the subject-matter of claims 1 to 12 involves an inventive step.

CLAIMS

1. Use of a bisphosphonic acid derivative, or a pharmaceutically acceptable salt or hydrate thereof, for the manufacture of a medicament for the prevention of secondary caries, wherein the secondary caries is at the interface between the natural dental material and a filling material.

2. The use according to claim 1, wherein the medicament is formulated as a depot or paste.

3. The use according to claim 1, wherein the bisphosphonic acid derivative is of the formula I

$$R^1\text{-}C(PO_3H_2)_2\text{-}R^2 \qquad (I)$$

wherein R^1 and R^2 may be independently selected from hydrogen, halogen, COOH, optionally substituted C_{1-12}-alkyl, optionally substituted aryl, optionally substituted C_{3-9}-cycloalkyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted C_{1-12}-alkyl-aryl, optionally substituted C_{1-12}-alkyl-C_{3-9}-cycloalkyl, optionally substituted C_{1-12}-alkyl-heteroaryl, heteroaryl, heterocyclyl, optionally substituted C_{1-12}-alkyl-heterocyclyl, amino, optionally substituted C_{1-12}-alkyl-amino, optionally substituted amino-C_{1-12}-alkyl, optionally substituted amino-C_{3-9}-cycloalkyl, optionally substituted C_{1-12}-alkyl-halide, optionally substituted C_{1-12}-alkyl-OH, optionally substituted C_{1-12}-alkyl-SH, alkoxy, optionally substituted C_{1-12}-alkyl-O-alkyl, C_{1-12}-alkyl-S-alkyl, optionally substituted C_{1-12}-alkyl-COOH, and optionally substituted C_{1-12}-alkyl-PO_3H_2, or a pharmaceutically acceptable salt or hydrate thereof.

4. The use according to any one of claims 1 to 3, wherein the pharmaceutically acceptable salt is the mono-, di-, tri-, or tetrasodium salt.

5. The use according to any one of claims 1 to 4, wherein the bisphosphonic acid derivative is methanehydroxybisphosphonic acid.

6. The use according to any one of claims 1 to 4, wherein the bisphosphonic acid derivative is ethane-1-amino-1,1-bisphosphonic acid.

7. The use according to any one of claims 1 to 6, wherein the medicament is a dental filling material.

8. The use according to claim 7, wherein the dental filling is made of amalgam or plastic.

9. The use according to claim 1, wherein the medicament is in the form of a depot included in a sealing material.

10. The use according to claim 1 or 2, wherein the medicament further comprises etidronate, pamidronate, alendronate, tiludronate, risedronate, zoledronic acid, clodronic acid, ibandronic acid, neridronate, olpadronate, incadronate, 1-Hydroxy-3-(1-pyrrolidinyl)propylidene]bisphoshonate, or [1-Hydroxy-2-imidazo-(1,2a)pyridin-3-ylethylidene]bisphosphonate.

11. Use of etidronate, pamidronate, alendronate, tiludronate, risedronate, zoledronic acid, clodronic acid, ibandronic acid, neridronate, olpadronate, incadronate, 1-Hydroxy-3-(1-pyrrolidinyl)propylidene]bisphoshonate, or [1-Hydroxy-2-imidazo-(1,2a)pyridin-3-ylethylidene]bisphosphonate for the preparation of a medicament for the prevention of secondary caries.

12. The use according to any one of claims 1 to 11, wherein the filling or medicament comprises the bisphosphonate in a concentration of 0.001 to 50 M.

13. A dental filling material comprising a bisphosphonic acid derivative, or a pharmaceutically acceptable salt or hydrate thereof, as defined in any one of claims 1-6.

14. A dental sealing material comprising a bisphosphonic acid derivative, or a pharmaceutically acceptable salt or hydrate thereof, as defined in any one of claims 1-6.

15. A dental depot comprising a bisphosphonic acid derivative, or a pharmaceutically acceptable salt or hydrate thereof, as defined in any one of claims 1-6.